REMARKS

Claims 69-73, 102, 106, 108-110 and 112-122 are pending in this application.

Applicants have amended the specification, as discussed below, in response to the Examiner's suggestions.

Applicants have amended claim 69 to recite a method for inducing tissue formation at a locus accessible to at least one progenitor cell of a mammal, wherein the tissue is selected from the group consisting of bone, cartilage, tendon/ligament and neural tissue. Support for this amendment appears, for example, at specification page 4, line 33 to page 5, line 1; page 13, lines 6-34 and page 30, lines 4-12.

Applicants have also amended claim 69 to recite that the morphogenic protein comprises a polypeptide selected from the group consisting of BMP-4, BMP-5, BMP-6, BMP-7 (OP-1), BMP-8, BMP-9, BMP-10, BMP-11, BMP-12, BMP-13, Dpp, Vg-1, COP-5 and COP-7. Support for this amendment appears, for example, in specification page 15, lines 15-16; page 16, lines 14, 18-19 and 28-34; page 24, lines 11-14; and page 28, lines 20-22 and 24-26.

Applicants have amended claim 106 to depend from claim 69 instead of claim 67, which was previously canceled.

Applicants have amended claims 108 and 109 to depend from claim 69 instead of claim 107, which is canceled.

Applicants have amended claim 109 to replace "osteogenic protein" with -- morphogenic protein --.

Applicants have amended claim 110 to replace "tendon/ligament-like" and "neural-like" with -- tendon/ligament -- and -- neural --, respectively. Support for this amendment appears, for example, at specification page 8, lines 27-32.

Applicants have amended claims 112 and 114 to delete the recitation of "BMP-2".

Applicants have amended claims 116-118, 120 and 121 to provide sufficient antecedent basis for the limitation "pharmaceutical composition" .

None of the amendments constitutes new matter.

THE OBJECTIONS

SPECIFICATION PAGES 71-73

The Examiner has objected to the specification because portions of pages 71-73 are missing and that appropriate correction is required.

Applicants submit herewith substitute specification pages 71-73 (see Appendix A), thus, obviating the objection.

SEQUENCE IDENTIFIERS

The Examiner has objected to the specification stating that the application is not fully in compliance with the sequence rules under 37 C.F.R. §§ 1.821-1.825. Specifically, the Examiner alleges that the specification fails to recite the appropriate sequence identifiers at each place where a sequence is discussed. Applicants disagree.

Applicants respectfully submit that the specification discloses 5 sequences for which a Sequence Listing was prepared and submitted on July 31, 2003. Each of the sequences provided in the specification is identified by an appropriate sequence

identifier. The identifiers are mentioned either in the sentences preceding or the sentences following each of the specific sequences. For example, the sequence identifiers for amino acid sequences COP5 and COP7 are SEQ ID NO: 2 and SEQ ID NO: 3, respectively, which are mentioned on page 24, lines 11-14 of the originally filed application. Accordingly, applicants request that the Examiner withdraw this objection.

THE REJECTIONS

35 U.S.C. § 102(b): Claims 69, 71, 106-112, 114 and 115

The Examiner has maintained the rejection of claims 69, 71, 106-112, 114 and 115 under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent 5,166,058 ("Wang"). The Examiner states that Wang teaches that BMP-2 may be used to induce bone formation and provides pharmaceutical compositions containing a therapeutically effective amount of a BMP-2 in a pharmaceutically acceptable vehicle or carrier. The Examiner further states that it is expected that a BMP-2 may act in concert with or perhaps synergistically with other related proteins and growth factors and that BMP-2s, such as BMP-2A and BMP-2B, may be combined with other agents including various growth factors such as epidermal

growth factor (EGF), platelet derived growth factor (PDGF), transforming growth factors (TGF-α and TGF-β) and insulin growth factor (IGF) beneficial to the treatment of bone defects. The Examiner also states that Wang discloses that "the compositions further include at least one other therapeutically useful agent such as the BMP proteins BMP-1, BMP-3, BMP-5, BMP-6 and BMP-7." The Examiner states that if BMP-2 may act in concert with or perhaps synergistically with a growth factor such as IGF-I, as taught by Wang, then by necessity, the IGF-1 present is at an effective concentration to "synergistically" stimulate the tissue inductive activity of the morphogenic protein.

Applicants have amended claim 69 (and therefore, claims dependent thereon) to recite a method for inducing tissue formation comprising a morphogenic protein selected from the group consisting of BMP-4, BMP-5, BMP-6, BMP-7 (OP-1), BMP-8, BMP-9, BMP-10, BMP-11, BMP-12, BMP-13, Dpp, Vg-1, COP-5 and COP-7. The claims, as amended, do not recite BMP-2. Accordingly, applicants request that the Examiner withdraw the novelty rejection.

35 U.S.C. § 103(a)

Claims 69 and 102: Wang in view of Kuberasampath I

The Examiner has rejected claims 69 and 102 under 35 U.S.C. § 103(a) as being obvious over Wang in view of WO 91/18558 ("Kuberasampath I"). The Examiner asserts that Wang teaches how to administer a composition comprising a carrier, a morphogen and IGF-I. The Examiner asserts that Kuberasampath I teaches a device comprising a carrier comprising heparin but does not teach a method of administering a composition comprising a carrier, a morphogen and IGF-I. The Examiner concludes that it would have been obvious to one of ordinary skill in the art to combine the two references to arrive at applicants' invention.

As described above, applicants have amended claim 69 (and therefore, claim 102) to recite a method for inducing tissue formation comprising the step of implanting a morphogenic device comprising a carrier, a morphogenic protein selected from the group consisting of BMP-4, BMP-5, BMP-6, BMP-7 (OP-1), BMP-8, BMP-9, BMP-10, BMP-11, BMP-12, BMP-13, Dpp, Vg-1, COP-5 and COP-7 and a morphogenic protein stimulatory factor selected from the group consisting of IGF-I, hydrocortisone, insulin and

parathyroid hormone, wherein said MPSF is at a concentration effective to synergistically stimulate the ability of the morphogenic protein to induce tissue formation from the progenitor cell.

Wang discloses the use of BMP-2 and the growth factor IGF-I for treating bone, cartilage and periodontal diseases. Wang also discloses that the BMP-2 "may act in concert with or perhaps synergistically with growth factors."

Kuberasampath I discloses a porous matrix which includes a cross-linked polymer of collagen and glycosaminoglycan, wherein the glycosaminoglycan may be heparin. Kuberasampath I does not disclose a heparin carrier as indicated by the Examiner. Rather, the heparin is crosslinked to the collagen. Therefore, the combination of Wang and Kubersampath I does not teach or suggest a method for inducing tissue formation as recited in the amended claims. Accordingly, applicant requests that the Examiner withdraw this obviousness rejection.

Claims 69 and 116: Wang

The Examiner has rejected claims 69 and 116 under 35 U.S.C. § 103(a) as being obvious over Wang. The Examiner states that Wang teaches that BMP-2 may be used to induce bone formation and provided pharmaceutical compositions containing a therapeutically effective amount of BMP-2 in a carrier. The Examiner further states that it is expected that a BMP-2 may act in concert with or perhaps synergistically with other related proteins and growth factors. The Examiner also states that Wang discloses BMP-2 may be combined with other agents beneficial to the treatment of bone defects including epidermal growth factor (EGF), platelet derived growth factor (PDGF), transforming growth factors (TGF-α and TGF-β) and insulin-like growth factor (IGF) or IGF-I. The Examiner also states that the Wang patent is silent with respect to the specific dosages recited in claim 116 but that it is not inventive to discover the optimum or workable ranges by routine experimentation.

As discussed above, applicants have amended claim 69 (and therefore, claim 116) to recite a method for inducing tissue formation comprising the step of implanting a morphogenic device

comprising a carrier, a morphogenic protein selected from the group consisting of BMP-4, BMP-5, BMP-6, BMP-7 (OP-1), BMP-8, BMP-9, BMP-10, BMP-11, BMP-12, BMP-13, Dpp, Vg-1, COP-5 and COP-7 and a morphogenic protein stimulatory factor selected from the group consisting of IGF-I, hydrocortisone, insulin and parathyroid hormone, wherein said MPSF is at a concentration effective to synergistically stimulate the ability of the morphogenic protein to induce tissue formation from the progenitor cell.

First, Wang only discloses that BMP-2 "may act in concert or perhaps synergistically with other related proteins and growth factors." Nothing in Wang teaches or suggests that IGF-I synergizes the tissue inductive ability of BMP-4, BMP-5, BMP-6, BMP-7 (OP-1), BMP-8, BMP-9, BMP-10, BMP-11, BMP-12, BMP-13, Dpp, Vg-1, COP-5 and COP-7, as claimed in the instant application. Second, nothing in Wang teaches or suggests that hydrocortisone, insulin or parathyroid hormone can synergize the tissue inductive ability of the claimed morphogenic proteins. Accordingly, applicants request that the Examiner withdraw this obviousness rejection.

Claims 69, 113 and 117: Wang in view of the Kuberasampath II and Reddi

The Examiner has rejected claims 69, 113 and 117 under 35 U.S.C. § 103(a) as being obvious over Wang in view of U.S. Patent 5,674,844 ("Kuberasampath II") and Reddi, A. H. et al., "Bone induction by osteogenin and bone morphogenic proteins", Biomaterials, 11: pp. 33-34 (1990) ("Reddi"). The Examiner states that Wang is silent with respect to the "synergistic" combination of BMP-7 and IGF-I and that Kuberasampath II provides methods and compositions for inhibiting loss of bone mass and/or for stimulating bone formation including a therapeutically effective morphogen. The Examiner further states that Kuberasampath II discloses that morphogens may be administered with other "co-factors" known to have a beneficial effect on bone remodeling including IGF-I." The Examiner states that Reddi teaches that the initiation of bone formation by osteogenin or BMPs is promoted by PDGF, TGF-β, IGF-1 and -2 and FGF. The Examiner concludes that one of ordinary skill in the art would have reasonably expected that the combination of OP-1 and IGF-I is synergistic. The Examiner also asserts claim 117 is obvious

because it is not inventive to discover the optimum or workable ranges by routine experimentation.

As discussed above and stated by the Examiner, Wang does not teach or suggest that the activity of any BMP other than BMP-2 may be synergized by IGF-I. Kubersampath II and Reddi do not remedy this deficiency. Kuberasampath II discloses that morphogens may be administered with co-factors including IGF-I and IGF-II. Reddi merely discloses that the initiation of bone induction is regulated by BMPs and may be promoted by PDGF, TGF-β, IGF-I and -II and FGF. Nothing in Wang in combination with Kuberasampath II and Reddi would provide the skilled worker in the art with a reasonable expectation that IGF-I, hydrocortisone, insulin and parathyroid hormone would synergistically stimulate the ability of a morphogenic protein selected from the group consisting of BMP-4, BMP-5, BMP-6, BMP-7 (OP-1), BMP-8, BMP-9, BMP-10, BMP-11, BMP-12, BMP-13, Dpp, Vg-1, COP-5 and COP-7, as recited in the claims of the instant application. In fact, applicants have demonstrated that some of the growth factors disclosed in Kuberasampath II and Reddi do not act synergistically with a morphogenic protein. Applicants have

discovered that TGF-β1 and IGF-II do not act synergistically with a BMP. Although TGF-βs were said to have certain bone growth activity, applicants have demonstrated that TGF-β1 does not stimulate OP-1 induced osteogenic induction. In fact, applicants have shown that TGF-β1 inhibits OP-1 activity. In addition, applicants have demonstrated that IGF-II does not stimulate OP-1 induced osteogenic induction. Accordingly, the combination of Wang, Kuberasampath II and Reddi does not render claims 69, 113 and 117 obvious.

Obviousness-Type Double Patenting

Claims 69, 71, 102 and 106-117

The Examiner has rejected claims 69, 71, 102 and 106-117 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-15 of United States patent 6,048,964 and claim 30 of United States patent 5,948,428.

Applicants remain ready to submit a terminal disclaimer in compliance with 37 C.F.R. § 1.321(c) upon an indication by the Examiner that all other rejections are withdrawn.

35 U.S.C. § 112, first paragraph

Claims 69, 71, 102 and 106-117

The Examiner has rejected claims 69, 71, 102 and 106-117 under 35 U.S.C. § 112, first paragraph for lack of enablement. The Examiner contends that applicants' specification discloses no more, and perhaps even less, than the prior art with respect to the claimed invention. Specifically, the Examiner contends that the only working examples in the present specification is the induction of alkaline phosphatase activity in FRC cells and that there is no established nexus evident in the prior art or in applicants' specification between the induction of alkaline phosphatase activity in FRC cells and the induction of any and/or all local tissue formation and/or the synergistic stimulation thereof. The Examiner also contends that the use of in vitro assay systems has proven not to be predictive of bone formation in vivo. The Examiner further contends that the claims encompass the regeneration of permanent cells that are retained throughout adult life and seem never to divide and which cannot be replaced if lost. The Examiner concludes that in view of the breadth of the claims, the limited amount of direction and

working examples and the unpredictability in the art, it would require undue experimentation for the skilled artisan to make and/or use the full scope of the claimed invention. Applicants traverse.

Applicants respectfully submit that the present application is enabling for the invention as claimed. First, in addition to the biological markers that may be used to determine tissue formation, the specification provides various examples describing animal models for testing bone, cartilage, tendon/ligament and neural tissue formation (see Examples 8-13). These animal models are used to demonstrate tissue formation in vivo and are predictive of tissue formation in the human patient.

Second, applicants submit that the alkaline phosphatase activity is predictive of bone formation. It has been extensively used to demonstrate, e.g., the activity of OP-1, which has been FDA approved for inducing bone formation in human patients.

Third, as stated in the Declaration of John C. Lee, ("Lee Declaration"), filed concurrently herewith, the ability of IGF-I to synergistically enhance the tissue inductive activity of

OP-1 in cartilage tissue has also been tested. Specifically, the Lee Declaration demonstrates that the combination of OP-1 and IGF-I synergistically induced the alkaline phosphatase activity in a primary culture of bovine articular cells (Lee Declaration, ¶¶ 6-8).

Applicants respectfully submit that the present application provides sufficient enablement for one skilled in the art to make and use the invention without undue experimentation. Accordingly, applicants request that the Examiner withdraw the rejection.

35 U.S.C. § 112, first paragraph

Claims 69, 71, 102 and 107-110, 115 and 116

The Examiner has rejected claims 69, 71, 102 and 107-110, 115 and 116 under 35 U.S.C. § 112, first paragraph for lack of written description. The Examiner contends that the terms "morphogenic" or "osteogenic" protein encompass a genus of polypeptides but that the specification fails to indicate what distinguishing attributes are shared by the members of the genus. The Examiner further contends that because the disclosure fails

to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the BMP subfamily of the TGF-β superfamily alone is insufficient to describe the genus.

Applicants traverse. The specification provides ample written description for "morphogenic protein" and "osteogenic protein." However, to expedite prosecution, applicants have amended the claims to recite that the morphogenic protein is selected from the group consisting of BMP-4, BMP-5, BMP-6, BMP-7 (OP-1), BMP-8, BMP-9, BMP-10, BMP-11, BMP-12, BMP-13, Dpp, Vg-1, COP-5 and COP-7. The specification provides ample written description for these proteins (see, e.g., specification page 15, lines 15-16; page 16, lines 14-34; page 24, lines 11-24; and page 28, lines 20-22 and 24-26). Accordingly, the Examiner's rejection has been obviated.

35 U.S.C. § 112, second paragraph

Claims 69, 71, 102, 107-110, 115 and 116

The Examiner has rejected claims 69, 71, 102 and 107-110, 115 and 116 under 35 U.S.C. § 112, second paragraph as being

indefinite. The Examiner contends that the terms "morphogenic" or "osteogenic" protein are indefinite because the "specification does not identify that material element or combination of elements which is unique to, and, therefore, definitive of 'morphogenic' or 'osteogenic' protein [such that] an artisan cannot determine what additional or material limitations are placed upon a claim by the presence of this element." Applicants traverse.

Applicants respectfully submits that the specification clearly defines what is intended by a "morphogenic protein" and an "osteogenic protein". However, to expedite prosecution, applicants have amended claim 69 (and therefore, claims dependent thereon) to recite that the morphogenic protein is selected from the group consisting of BMP-4, BMP-5, BMP-6, BMP-7 (OP-1), BMP-8, BMP-9, BMP-10, BMP-11, BMP-12, BMP-13, Dpp, Vg-1, COP-5 and COP-7. Further, applicants have amended claims 108 and 109 to cancel recitation of an osteogenic protein. Accordingly, applicants' rejection has been obviated.

Claim 110

The Examiner has rejected claim 110 under 35 U.S.C. § 112, second paragraph as being indefiniteness. The Examiner contends that it is unclear what applicant intends to cover by the recitation "tendon/ligament-like" or "neural-like" tissue.

Applicants have amended claim 110 to replace "tendon/ligament-like" and "neural-like" with "tendon/ligament" and "neural." Support for this amendment is provided in the specification, for example, on page 8, lines 27-32. Accordingly, applicants request that the Examiner withdraw this rejection.

Claims 116 and 117

The Examiner has rejected claims 116 and 117 under 35 U.S.C. § 112, second paragraph as being indefinite. The Examiner contends that there is insufficient antecedent basis for the limitation "pharmaceutical composition."

Applicants have amended claims 116 and 117 to provide the appropriate antecedent basis for the limitation "pharmaceutical composition," thus obviating the rejection.

Claims 69, 71, 102 and 106-117

The Examiner has rejected claims 69, 71, 102 and 106-117 under 35 U.S.C. § 112, second paragraph as being indefinite. The Examiner contends that the term "local tissue formation" is indefinite because the instant specification does not identify that material element or combination of elements which is unique to, and, therefore, definitive of ""local tissue formation" such that an artisan cannot determine what additional or material limitations are placed upon a claim by the presence of this element. Applicants traverse.

Applicants have amended the claims to recite "tissue formation" instead of "local tissue formation," thus obviating the rejection.

CONCLUSION

In view of the above, applicants respectfully request consideration and early allowance of the pending claims in this application.

Respectfully submitted,

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